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CARDIAC FUNCTION AND HEART FAILURE

CHRONIC KIDNEY DISEASE-INDUCED CARDIAC FIBROSIS IS AMELIORATED BY REDUCING CIRCULATING LEVELS OF A NON-DIALYSABLE UREMIC TOXIN, INDOXYL SULFATE

ACC Oral Contributions

Ernest N. Morial Convention Center, Room 243

Monday, April 04, 2011, 2:15 p.m.-2:30 p.m.

Session Title: Cardiomyopathy: Bench to Bedside

Abstract Category: 22. Cardiomyopathies/Myocarditis/Pericardial Disease

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Background: Cardiovascular death commonly occurs in chronic kidney disease. Indoxyl sulfate (IS), a uremic toxin, has been demonstrated in vitro as a contributory factor in cardiac fibrosis, a typical pathological finding in uremic cardiomyopathy. This study aimed to determine if cardiac fibrosis is reversible by lowering serum IS levels using an oral charcoal adsorbent, AST-120.

Methods: Subtotal-nephrectomised (5/6-STNx) Sprague-Dawley rats were randomized to receive either AST-120 (AST-120, n=13) or no treatment (vehicle, n=17) for 12 weeks. Sham operated rats (n=12) were used as controls. Serum IS level was measured at baseline and 12 weeks. Cardiac and renal function was assessed prior to sacrifice at 12 weeks. Tissues were assessed for pathological changes using histological methods, western blot analysis and real-time PCR.

Results: Compared to sham, STNx animals had significantly higher serum creatinine and urine total protein levels, and reduced GFR/kg. Early left ventricular (LV) diastolic dysfunction was demonstrated by an increase of the peak velocity of atrial filling [A and A' waves] and a decrease of E/A and E'/A' ratios obtained by echocardiography. This was accompanied by a 4.5-fold increase in serum IS ($p<0.001$) as well as elevated tail-cuff blood pressure ($p<0.001$) and heart weight ($p<0.001$). Increased LV fibrosis ($p<0.001$), gene expression of pro-fibrotic (TGF- β , CTGF) and hypertrophic (ANP, β -MHC and α -skeletal muscle actin) markers, as well as TGF- β and phosphorylated NF- κ B protein expression were observed in STNx+vehicle rats. Treatment with AST-120 reduced serum creatinine (by 35%, $p<0.05$) and urine total protein (by 23%, $p<0.05$) vs vehicle whilst having no effect on blood pressure (AST-120=227 \pm 11 vs vehicle=224 \pm 8 mmHg, ns) and heart weight. Serum IS was reduced with AST-120 (by 79%, $p<0.001$) which was accompanied by reduced LV fibrosis (by 35%, $p<0.01$) and TGF- β and phosphorylated NF- κ B protein expression (back to sham levels, $p<0.05$) despite no significant change in LV function.

Conclusions: STNx resulted in increased cardiac fibrosis and circulating IS levels. Reduction of IS with AST-120 normalises cardiac fibrosis, in a blood pressure independent manner.